REMARKS

I. Status of the claims

Claims 20-25 and 27 are pending. Claim 26 has been cancelled without prejudice or disclaimer. Of course, Applicant reserves the right to file one or more continuing applications to the cancelled subject matter.

Applicant acknowledges the Examiner's withdrawal of the rejection of claims 24 and 25 under 35 U.S.C. § 112, first paragraph.

II. The antecedent basis in claim 25 has been corrected

The Examiner rejected claim 25 as being indefinite because, in depending from claim 23, there is no "antecedent basis [in claim 25] for 'the tyrosine kinase receptors'." Office Action at page 2. Applicant asserts that claim 25 should depend from claim 24, and has amended claim 25 accordingly. Therefore, Applicant respectfully requests that the Examiner withdraw this rejection.

III. Claims 26 and 27 are enabled

The Examiner rejected claims 26 and 27 under 35 U.S.C. § 112, first paragraph, alleging that "because the claimed methods require administering the labeled ligand to blood, and because most bodily fluids are in equilibrium with the blood, the ligand would be detectable in most body fluid compartments. Thus, it would require undue experimentation to make a method as claimed because one of skill in the art would first have to determine what levels of ligand constitutes an 'abnormal presence' of the ligand in a body fluid compartment." Office Action at page 4.

Without acquiescing to the Examiner's position, Applicant has cancelled claim 26, and deleted recitation of "blood" and "serum" from claim 27. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

IV. Claims 20-23 are not rendered obvious in light of Boocock *et al.*, in view of Ferrara

The Examiner rejected claims 20-23 under 35 U.S.C. § 103(a) as unpatentable over Boocock, *J. Nat. Cancer Inst.*, 87(7), p.506-516, 1995, in view of Ferrara (WO 94/10202), because, according to the Examiner, it would have been obvious to "have made a method for in vivo detection of VEGF for the detection of metastasis at a site distal from the primary tumor, and also to have made a method that further comprises detection of angiogenic tyrosine kinase receptors, such as flt." Office Action at page 5.

Furthermore, the Examiner alleges that "one would have been motivated to have made such a method because Ferrara teaches that it is desirable to have a means for assaying for the presence of VEGF in pathological conditions, such as cancer, and because Boocock teaches that VEGF is present in metastatic tumors." Office Action at page 5.

Applicant respectfully disagrees and traverses the rejection. Ferrara teaches that an antibody or receptor "is useful for *in vivo* imaging" (page 12, line 26). The Examiner acknowledges that "Boocock fails to explicitly teach an *in vivo* method of detection of VEGF." Office Action at page 5. Moreover, Boocock does not teach or suggest that VEGF can be used to detect *metastasis*.

The disclosure of Boocock is limited to the detection of VEGF in tumors ***whose status is already identified as either primary tumors or metastases***. Indeed, the Examiner implicitly acknowledges that this is so by stating, parenthetically, that "a sample **of a tissue metastasis** is by definition a site that is distal from a primary tumor." Office Action at page 5. Thus, the sample(s) examined by Boocock *et al.* were already classified as metastatic tissues at the time those studies were made. To be sure, Boocock *et al.* states in the abstract that VEGF expression was "localized by *in situ* hybridization and immunohistochemistry in frozen sections of primary tumors from five patients with ovarian carcinoma **and from metastases of ovarian carcinoma**" (emphasis added). Boocock *et al.* does not identify unknown tissues as metastatic, but correlates VEGF expression in ***already-identified*** metastatic samples.

Furthermore, Boocock *et al.* only shows detection of VEGF in cultured tumor cells, and does not disclose an *in vivo* detection of VEGF. Therefore, contrary to the Examiner's assertion, Boocock *et al.* fails to teach or suggest VEGF as a detector of metastasis, and simply does not disclose a method of detecting "the presence of metastasis in [a] human," as presently claimed.

No combination of Ferrara and Boocock *et al.* would prompt the skilled artisan to devise a method for determining whether a sample in a person's body was metastatic. It is all the more telling that this is so, since Ferrara was available to Boocock *et al.* prior to the latter's studies. However, Boocock *et al.* did not rely on the teachings of Ferrara *et al.*, did not use any "*in vivo* imaging" techniques, and furthermore did not propose or contemplate a method for determining the metastatic state of undiagnosed tissues, as prescribed by the presently claimed invention.

Thus, the combined prior art fails to recognize the critical importance of detecting an abnormal presence of VEGF at a site distal from a primary tumor for ***diagnosing*** a metastatic potential of a primary tumor. Accordingly, the combination of Boocock *et al.* in view of Ferrara does not render Applicant's claimed invention as obvious, and Applicant respectfully requests that the Examiner withdraw this rejection.

V. Conclusion

In conclusion, Applicant respectfully requests withdrawal of all the obviousness rejections. Applicant believes that the present application is now in condition for allowance and favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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MARKED-UP VERSION OF THE CLAIMS

25. (Once amended) The method of claim **24** [23] wherein the tyrosine kinase receptors are chosen from the group consisting of the *KDR/flk-1* receptor, the *flt-1* receptor, and/or the *tek/tie-2* receptor.

27. (Once amended) The method of claim 25, wherein **the site distal from a primary tumor is a** [the] body fluid [is] selected from the group consisting of [blood, serum,] urine, lymph and cerebrospinal fluid.